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ORIGINAL ARTICLE

The role of serum testosterone to prostate-specific antigen ratio as a predictor of prostate cancer risk

Cenk Gurbuz*, **Lutfi Canat, Gokhan Atis, Bayram Guner, Turhan Caskurlu**

Department of 2nd Urology, Istanbul Goztepe Training and Research Hospital, Istanbul, Turkey

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Abstract We analyzed the ratio of serum total testosterone (sTT) to prostate-specific antigen (PSA) as a predictor of prostate cancer risk. One-hundred-four consecutive men with a normal digital rectal examination and a serum PSA level of 2.5–10 ng/ml underwent transrectal ultrasonography-guided biopsy using a 10-core scheme. The sTT level was determined before the procedure using a chemiluminescent assay, and the ratio of sTT to PSA (sTT/PSA) was calculated after transforming sTT measurements from ng/dL to ng/mL. The overall cancer detection rate was 17.3%. The median sTT level was 332 ng/dl in men with cancer and 413 ng/dL in those without ($p = 0.032$). The median sTT/PSA ratio in these groups was 0.55 and 0.74, respectively ($p = 0.035$). The receiver operator characteristic (ROC) method was used to evaluate the properties of the sTT/PSA ratio, with testosterone and PSA as predictors of prostate cancer risk. The accuracy of the sTT/PSA ratio in prostate cancer diagnosis, represented by the area under the curve (AUC), was 0.739 (95% CI 0.640–0.823, $p < 0.05$). Optimizing the sensitivity and specificity of the sTT/PSA ratio using the ROC provided a cutoff point of 0.60, which corresponded to 82% sensitivity and 62% specificity. When the patients were divided into normal- and low-sTT level groups according to testosterone value (300 ng/dl), the probability of detecting prostate cancer was 3.3-fold higher in hypogonadal men as compared with eugonadal men. These results support the use of the sTT-to-PSA ratio for predicting the risk of prostate cancer and increasing the specificity of PSA measurement.

Introduction

The introduction of serum prostate-specific antigen (PSA) screening has made the early detection of prostate cancer possible. Nonetheless, serum PSA is not a perfect disease marker, most notably because of its low specificity. PSA elevations can be caused by both prostate cancer and nonmalignant diseases, such as benign prostatic hyperplasia

* Corresponding author. Kısıklı mahallesi, İlkkent Camlık Sitesi, B Blok D 12, Üsküdar, Istanbul, Turkey.
E-mail address: gurbuzcenk@yahoo.com (C. Gurbuz).

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or chronic prostatitis [1]. Unnecessary biopsies are still an important clinical issue.

The potential clinical applications of serum total testosterone (sTT) determination in patient screening, diagnosis and the management of prostate cancer have been evaluated in the literature [2]. Currently, the association of serum testosterone with prostate cancer is incompletely understood. Studies comparing circulating male sex hormone levels between subjects with and without prostate cancer have produced widely varying results [3,4]. The usefulness of using the sTT/PSA ratio as a predictor of prostate cancer risk was recently suggested by Karamanolakis et al. [5]. Rhoden et al. [6] confirmed its usefulness in hypogonadal men with low levels of serum PSA. Morote et al., however, failed to confirm that it is a useful tool to increase the specificity of PSA in eugonadal or hypogonadal men [7].

The main objective of the present study was to analyze the relationship between sTT and PSA levels and the risk of prostate cancer in a consecutive cohort of eugonodal and hypogonadal men with normal DRE and a serum PSA level of 2.5–10 ng/ml.

Methods

The study was executed in accordance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable regulatory guidelines. Between October 2008 and March 2010, 104 patients were included in this study. All participants provided their written informed consent. The mean patient age was 63.7 years (42–73 years). Patients with elevated PSA levels (2.5–10 ng/ml) who underwent a transrectal ultrasound prostate biopsy were included in the study. Exclusion criteria included the following:

- men on medications known to lower PSA, such as finasteride or dutasteride, or any antibiotic treatment;
- patients receiving anticoagulant therapy;
- patients who had an indwelling Foley catheter, a symptomatic or asymptomatic urinary tract infection, bleeding disorders, acute prostatitis before prostate biopsy, a previous prostatic biopsy or prostate surgery; and
- total length of tissue obtained via biopsy of <10 cm.

Total serum PSA levels, with a reference range of 0.003–100.0 ng/mL, were measured by electrochemiluminescence immunoassay (Modular Analytics E170, Roche Diagnostics, Switzerland; interassay CV <3.2%). The sTT levels, with a reference range of 2.5–1500.0 ng/dl, were determined using a solid-phase, competitive chemiluminescent enzyme immunoassay, using the Immulite 2500 automated analyzer device (DPC Inc., Los Angeles, CA, USA; interassay CV <4.1%.

Blood samples were obtained between 08:00 and 10:00 hours and processed immediately. Men with sTT <300 ng/dl were considered hypogonadal [6]. The sTT to PSA ratio was calculated after transforming sTT levels into ng/mL, the units in which PSA is normally expressed.

The biopsy procedure was performed on patients in the left lateral decubitus position using a Toshiba Fabio scanner with an attached 7.5 MHz biplanar probe (Toshiba, Tokyo, Japan). The 10 core prostate biopsies (traditional sextant biopsy cores and four laterally-placed biopsies in the right and left apex and mid-portion of the prostate gland) were obtained with a spring-loaded biopsy gun (C. R. Bard, Inc., Covington, Georgia, USA) and an 18-gauge Tru-cut biopsy needle (UK Medical, Sheffield, UK). The core-sampling notch was approximately 17 mm long and 12 mm in diameter.

Statistical evaluation

Data are presented as mean standard deviation (SD). The differences between group variables were evaluated by unpaired t-test, and the Chi-square test was used to evaluate qualitative variables. A receiver operator characteristic (ROC) curve analysis was used to evaluate the properties of the sTT/PSA ratio as a predictor of prostate cancer risk and identify an optimal cutoff point for the test in this particular study population. Further analysis of the sTT/PSA ratio was performed based on cutoff values obtained by an ROC curve method. Statistical significance was considered at $p < 0.05$.

Results

There were 86 men (82.7%) with benign prostate biopsies and 18 (17.3%) with prostate cancer. There were no significant differences between these groups with regard to age, prostate volume and PSA level. The total testosterone values and sTT/PSA ratio, however, were found to be statistically lower in the prostate cancer group (Table 1). The characteristics of men with prostate cancer are presented in Table 2. When the patients are divided to normal- and low-sTT level groups according to testosterone value (3 ng/ml), the probability of detecting prostate cancer was significantly higher (age-adjusted odds ratio [OR] 3.3; 95% confidence interval [CI]: 1.15–9.43) in hypogonadal men as compared with eugonadal men (25.9% vs. 14.3%, $p = 0.044$).

Table 1 Clinical and laboratory features in men with and without prostate cancer.

	Benign biopsy ($n = 86$)	Prostate cancer ($n = 18$)	p
Age (yr)	63.45 ± 6.57	64.06 ± 5.66	0.719
PSA (ng/ml)	6.27 ± 1.86	6.75 ± 2.00	0.333
Volume (cm^3)	51.97 ± 24.46	49.17 ± 19.87	0.385
Total testosterone (ng/ml)	4.13 ± 1.52	3.32 ± 1.00	**0.032**
Testosterone/PSA	0.74 ± 0.38	0.55 ± 0.28	**0.035**

Bold values represent values with $p < 0.05$.

Table 2 Characteristics of men with prostate cancer.

Patient number	Age (years)	PV (cm^3)	PSA (ng/ml)	Testosterone (ng/ml)	sTT/PSA	Gleason grade
1	59	41	7.7	**1.93**	0.205	3 + 3
2	71	30	6.1	**2.05**	0.336	3 + 3
3	66	30	9.0	**2.05**	0.227	5 + 5
4	62	36	4.2	**2.42**	0.576	3 + 3
5	53	21	5.0	**2.43**	0.486	3 + 3
6	65	30	7.0	**2.49**	0.355	4 + 4
7	66	75	6.9	**2.92**	0.423	3 + 3
8	69	40	5.3	3.02	0.569	4 + 4
9	50	43	7.6	3.17	0.417	3 + 3
10	67	48	5.1	3.44	0.674	4 + 4
11	70	40	8.6	3.61	0.419	3 + 3
12	68	24	2.7	3.67	0.136	3 + 3
13	61	60	6.3	3.83	0.607	3 + 3
14	68	35	8.0	3.94	0.492	4 + 4
15	65	38	9.9	4.08	0.412	3 + 3
16	67	65	9.0	4.54	0.504	3 + 3
17	60	26	4.4	5.00	0.111	3 + 3
18	66	23	8.7	5.40	0.627	3 + 4

PSA — prostate-specific antigen; PV — prostate volume; sTT — serum total testosterone.
Bold numbers indicates abnormal values.

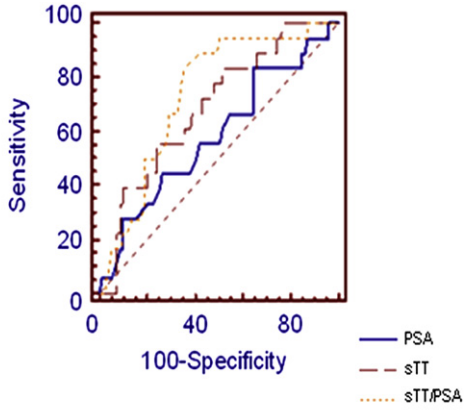
The frequency of high-grade cancer (Gleason score >6) was reported as 28% (2/7) and 36% (4/11) in hyopogonadal and eugonodal patients, respectively ($p = 0.648$).

The ROC curve method was used to evaluate the properties of the sTT/PSA ratio, with testosterone and PSA levels as predictors of prostate cancer risk. It was used to identify an optimal cutoff point for the sTT/PSA ratio in this particular study population. The accuracy of the sTT/PSA ratio in the presence prostate cancer diagnosis, represented by the area under the curve (AUC), was 0.739 (95% CI: 0.640—0,823, $p < 0.05$). Optimizing the sensitivity and specificity of the sTT/PSA ratio using the ROC provided a cutoff point of 0.60, which corresponded to 82% sensitivity and 62% specificity (Fig. 1). Four of the 15 men with high-grade cancer (Gleason score >6) had sTT/PSA ratio of values <0.60, which is the threshold value proposed by our study.

Discussion

Although the pathological and therapeutic significance of the androgen axis is known, there is currently no widely recognized application of serum testosterone determination in determining prostate cancer risk using PSA level. There is substantial controversy in the literature regarding the association between testosterone levels and prostate cancer risk.

The usefulness of the sTT/PSA ratio as a predictor of prostate cancer risk was suggested by Karamanolakis et al. [5]. These authors analyzed a group of 97 patients with a serum PSA level of 3—10 ng/mL who underwent a sextant transrectal ultrasound-guided biopsy. We observed significantly lower sTT levels and significantly lower sTT/PSA ratios in patients with prostate cancer than in those who provided biopsies that were free of any sign of cancer. Using 0.95 as the threshold level for sTT/PSA, the sensitivity was 96.5% and the specificity was 81% for the diagnosis of prostate cancer. Rhoden et al. [6] analyzed the usefulness of the sTT/PSA ratio in 184 consecutive men with symptomatic hypogonadism and a PSA level of ≤4.0 ng/ml that underwent sextant biopsy. The sTT/PSA ratio was found to be inversely related to prostate cancer risk. A sTT/PSA ratio of <1.8 was diagnostic for prostate cancer, while values below this threshold were associated with an odds ratio of 3.0 for prostate cancer. These two studies [5,6] support the determination of a testosterone-to-PSA ratio as an adjunctive diagnostic test in patients with mild PSA elevations or patients with hypogonadism and borderline PSA values, albeit with different thresholds for these two groups. Morote et al. [7], however, failed to reproduce these results in patients with PSA levels of



PSA – prostate-specific antigen; sTT – serum total testosterone

Figure 1. A receiver operator characteristic (ROC) curve for sTT/PSA ratio, testosterone and PSA in the prediction of prostate cancer.

4.1—20 ng/ml. Their study did not support the use of a sTT/PSA ratio as a predictor of prostate cancer risk in clinical practice. Furthermore, Morote et al. also failed to detect any utility for this ratio in hypogonadal men with PSA levels of 4.1—20 ng/ml.

There have been many attempts to characterize the influence of the prostate on serum hormone levels. Some studies suggest that high testosterone levels are associated with an increased risk of prostate cancer [8,9]. Yano et al. [10] reported that the positive rate of prostate biopsy in patients with a sTT level >5.5 ng/ml was significantly higher than in patients with sTT <5.5 ng/ml. Our findings were inconsistent with these results. The mechanisms that lead to the endocrine changes observed in men with prostate cancer are not clear. Imamoto et al. recently reviewed 10 modest-sized prospective studies to determine the role of testosterone in the pathogenesis of prostate cancer. Results from these studies have been inconclusive [11].

Within the diagnostic ''gray zone'' (PSA of 2.5—10 ng/ml), the risk of prostate cancer detectable by modern biopsy protocols is around 25%, making unnecessary biopsies an important clinical issue [12]. The overall rate of prostate cancer detection in the first round of biopsy was approximately 20% in the present study. The biopsy scheme was modified by increasing the minimum number of cores from eight to 10. A 12-core biopsy was sometimes recommended in the second-round biopsy. Previous studies that supported the use of the sTT/PSA ratio were criticized because sextant biopsies were used and a significant number of prostate cancers may have been missed. The strengths of this present study include its evaluation of 10 biopsy cores per patient.

It is difficult to compare the present study with other studies because PSA and sTT levels had different distributions. The diagnosis of hypogonadism is based on a sTT level <3 ng/ml in the present study. The risk of prostate cancer detection increased 3.3-fold for hypogonadal men compared with eugonodal men in the current study. Hoffman et al. [13] reported that in patients with low compared to normal free testosterone, there was an increased mean percentage of biopsies that showed cancer (43% vs. 22%, $p = 0.013$). However, Rhoden [6] did not show any relationship between total testosterone level and an increased risk of prostate cancer.

The association between low serum testosterone and high-grade prostate cancer is not clear in the literature [14,15]. Several hypotheses suggest why aggressive tumors may be more common in men with low testosterone. The first hypothesis states that prostate cancer inhibits androgens through negative feedback mediated by inhibin, PSA and dihydrotestosterone [16]. According to another hypothesis, the hormonal milieu might be varied enough to disrupt the normal growth and maintenance of prostatic tissue, while compensatory hyperplasia that results when the prostate atrophies might lead to cell mutation and the consequent selection of androgen-independent, aggressive prostate cells [17]. Previous studies have indicated that a lower sTT level might represent a marker for more aggressive disease [18,19]. In the present study, we did not observe any relationship between high-grade tumors and low testosterone levels. This variation may be due to the relatively small patient cohort.

Sex steroid hormones are thought to contribute to the growth, differentiation, and progression of prostate cancer. We only measured plasma concentrations of total testosterone. Total testosterone may not represent the true level of the biological male sex hormone. The possible associations between free testosterone, dihydrotestosterone, androstanediol, estradiol, and sex hormone-binding globulin and prostate cancer are not clear [19]. We did not focus on sex steroid hormone indices other than total testosterone.

There are some limitations of this study that we need to address, including the limited number of patients involved and the fact that not all of the biopsies were performed by a single person. We did not assess the role of the sTT/PSA ratio in making a decision regarding the second round of biopsies after a negative first biopsy round. There is no consensus on the cutoff values to be used for the sTT/PSA ratio. In the present study, a sTT/PSA ratio cutoff point of 0.6 was used, whereas this value was 0.95 for Karamanolakis et al. [5] and 1.8 for Rhoden et al. [6]. The value that is most appropriate can only be determined through large clinical trials. Measuring testosterone and calculating the sTT/PSA ratio may help us to identify men at increased risk of prostate cancer and to improve diagnostic accuracy in men with otherwise borderline PSA.

There are inconsistent results in the literature as to whether testosterone measurement is useful in prostate cancer screening strategies. The present study suggests that the sTT/PSA ratio might be considered a predictor of the risk of prostate cancer. Within the diagnostic ''gray zone '' (PSA of 2.5—10 ng/ml), the rate of prostate cancer detection was found to be higher in hypogonadal compared to eugonadal men. Our study showed that the sTT/PSA ratio seems to be useful in detecting prostate cancer risk. Despite this, further evaluation of serum testosterone to improve the specificity of PSA testing is warranted.

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